PATENT
Attorney Docket No. 054160-5060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: **Tsuneji Suzuki *et al.***	Confirmation No. **7720**
Application No. **10/049,666**	Group Art Unit: **1615**
Filed: **February 15, 2002**	Examiner: **Gollamudi S. Kishore**
Title: **Pharmaceutical Agent Comprising a Benzamide Derivative as Active Ingredient**	Date: February 2, 2007

APPELLANTS' BRIEF UNDER 37 C.F.R. § 41.37

This brief is in furtherance of the Notice of Appeal filed in the above-identified patent application on August 2, 2006 and a Response under 37 C.F.R. 1.116 filed on December 4, 2006 under the next business day rule. A fee of $500.00 as required under 37 C.F.R. §41.20(b)(2) is being filed concurrently herewith. The period for filing this brief has been extended from December 2, 2006 to February 2, 2007 by the filing of a petition for a two-month extension of time and authorization for fee payment.

02/05/2007 SZEWDIE1 00000090 500310 10049666
01 FC:1255 1140.00 DA

02/05/2007 SZEWDIE1 00000090 500310 10049666
02 FC:1402 500.00 DA

1. The Real Party in Interest

The real party in interest in this appeal is Schering Aktiengesellschaft of Berlin, Germany.

2. Related Appeals and Interferences

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

3. Status of Claims

The status of the claims is as follows upon filing of this Appeal Brief:

Claims cancelled: 1 to 43

Claims withdrawn from consideration but not canceled: None

Claims pending: 44 to 49

Claims objected to: None

Claims allowed: None

Claims rejected: 44 to 49

The claims on appeal are 44 to 49.

4. The Status of Amendments

Appellants filed an Amendment under 37 C.F.R. § 1.114 on December 9, 2005 in which claims 1 to 43 were canceled and new claims 44 to 49 were added. As such, Appellants submit that these claims are the currently pending claims of record. The claims listed in the claims appendix herein reflect the claim amendments of the aforementioned Amendment under 37 C.F.R. § 1.114.

5. Summary of Claimed Subject Matter

Aspects of Appellants' present invention relate generally to pharmaceutical formulations of any of three specific benzamide compounds or their pharmaceutically acceptable salts. These

claimed pharmaceutical formulations unexpectedly stabilize the benzamide compounds against degradation. Appellants' invention, as summarized below, is described in detail at page 1, line 27 to page 3, line 2 of the specification with the unexpected results indicated, *inter alia*, in Tables 1-8.

In accordance with the exemplary embodiment of the invention of independent claim 44, a pharmaceutical formulation of a benzamide compounds of Formula (1) includes an excipient selected from the recited group of suitable excipients, a lubricant selected from the recited group of suitable lubricants, a disintegrant selected from the recited group of suitable disintegrants and at least one member selected from the recited group of suitable amino compounds and inorganic bases. Support for claim 44 may be found in Appellants' specification at, *inter alia*, page 3, lines 3-17; page 6, line 33 to page 7, line 10 and page 7, lines 27-37.

In accordance with the exemplary embodiment of the invention of independent claim 46, a pharmaceutical formulation of a benzamide compound of Formula (1) includes at least one solvent selected from the recited group of suitable solvents and at least one member selected from the recited group of organic acid salts, amino compounds and inorganic bases. Support for claim 44 may be found in Appellants' specification at, *inter alia*, page 3, lines 3-17; page 7, lines 15-37 and page 16, Table 7.

6. Grounds of Rejection to be Reviewed on Appeal

Whether claims 44-49 are unpatentable under 35 U.S.C. § 103(a) as obvious over European Patent Application No. 0847 992 to Suzuki *et al.* ("Suzuki").

Whether claims 44-49 are unpatentable under 35 U.S.C. § 103(a) as obvious over European Patent Application No. 0847 992 to Suzuki *et al.* in view of the International Cosmetic Ingredient Dictionary and Handbook ("the Dictionary and Handbook").

Whether claims 44-49 are unpatentable under 35 U.S.C. § 103(a) as obvious over European Patent Application No. 0847 992 to Suzuki *et al.* in view of U.S. Patent No. 5,681,584 to Savastano *et al.* ("Savastano").

7. Argument

Appellants respectfully assert that the rejections under 35 U.S.C. §103(a) are improper and should be reversed.

A. Independent Claims 44 and 46

With respect to independent claim 44, Appellants respectfully assert that the applied art does not teach or suggest a combination of

(1) a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof;

(2) an excipient selected from the group consisting of lactose, lactose anhydride, D-mannitol, corn starch, and crystalline cellulose;

(3) a lubricant selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, and talc;

(4) a disintegrant selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium; and

(5) at least one member selected from the group consisting of an amino compound and an inorganic base,

wherein

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

With respect to independent claim 46, Appellants respectfully assert that the applied art does not teach or suggest a combination of

(1) a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof;

(2) at least one solvent selected from the group consisting of propylene glycol, dimethylacetamide, and a polyethylene glycol; and

(3) at least one member selected from the group consisting of an organic acid salt, an amino compound and an inorganic base;

wherein

the organic acid salt is at least one member selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

1. Rejection of Claims 44 and 46 under 35 U.S.C. 103(a) over Suzuki

The Office Action dated March 2, 2006 asserts that Suzuki teaches Appellants' claimed benzamide derivative and "generally used diluents or excipients, such as binders, extenders, fillers, moisturizers, disintegrants, surfactants, and lubricants." It is further asserted that Suzuki teaches a tablet formulation of the described benzamide derivative and that "in the tabletting art, the commonly used additives are a binder to bind the small amounts of the active ingredient, a disintegrants (*sic*) which enables the tablet to disintegrate in the system, a lubricant, amino compounds and buffering agents such as phosphates." Accordingly, the Office Action finds Appellants' claimed formulation obvious over Suzuki.

Appellants respectfully disagree with the obviousness rejections asserted by the Office Action. Suzuki does not teach or suggest pharmaceutical formulations comprising a benzamide compound of formula (1) in combination with the specific additives as claimed in independent claims 44 and 46. Suzuki merely provides a generalized and undifferentiated list of additives,

such as those listed at page 46, which may potentially be used for pharmaceutical formulations of various types. For example, regarding a tablet formulation, Suzuki states the following:

> "For preparing tablets, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as lactose, glucose, starch, calcium carbonate, kaoline, crystalline celluloses and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellacs, methyl cellulose and polyvinyl pyrrolidone; disintegration retarders such as sucrose, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch; absorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates and polyethylene glycol." (page 46, lines 9-16)

Without additional guidance, a person of ordinary skill in the art would not be motivated by the above list of additives to prepare the particular formulations claimed in independent claim 44 that contain a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an excipient selected from the group of specifically recited excipients; a lubricant selected from the group of specifically recited lubricants; a disintegrant selected from the group of specifically recited disintegrants; and at least one of an amino compound and an inorganic base selected from the group of specifically recited amino compounds and inorganic bases.

Further, there would be no motivation to prepare the particular formulations claimed in claim 46 by Appellants that contain a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof in combination with at least one solvent selected from the group of specifically recited solvents; and at least one of an organic acid salt, an amino compound and an inorganic base selected from the group of specifically recited organic acid salts, amino compounds and inorganic bases. Appellants note that Suzuki does not teach or suggest such a combination as recited in the formulation of Appellants' claim 46.

Appellants' claimed formulations also have unexpected results associated with them. These unexpected results are based on Appellants' observation that select benzamide compounds, while stable *per se* (*i.e.*, in the absence of various additives), may become unstable when present in a pharmaceutical formulation containing commonly used excipients and further, that some of these excipients accelerate the degradation of the benzamide compounds while other commonly used excipients do not. No one before Appellants has made these observations. Further, Appellants have exploited these findings by preparing and claiming pharmaceutical formulations that promote stabilization of these benzamide compounds.

As an example of these unexpected results, a portion of Table 1 is shown below (with additional examples listed in Table 1 as it appears in Appellants' specification at page 11). Table 1 lists the percent degradation of a benzamide compound encompassed by independent claim 44 in the presence of some commonly used excipients under the indicated conditions. The percent degradation was measured by high-pressure liquid chromatography (HPLC) analysis of each of the tested formulation mixtures. An inventor declaration under 37 C.F.R. 1.132 by Mr. Masahiro Sakabe, attesting to the significance of the observed data, was previously submitted to the U.S. Patent Office in a response filed on December 4, 2006. A copy of the declaration is attached herein in the Evidence Appendix.

Table 1. % Degradation of various powders containing a benzamide compound + additive

Additive	60°C air-tight for 4 weeks	40°C open at 75% relative humidity for 3 months
none	0.18	0.19
D-mannitol	0.21	0.21
partially gelatinized starch	0.21	0.34
hydroxypropyl cellulose	0.20	0.20
magnesium stearate	0.22	0.20
lactose	0.55	0.44
titanium oxide	1.75	0.82
light-weight silicic acid anhydride	5.87	10.01
magnesium aluminum metasilicate	17.94	5.45

As shown in Table 1 above, a formulation of a benzamide compound with an additive that results in a degradation value of, for example, 0.20% at 60°C (*i.e.,* a hydroxypropyl cellulose formulation) compares favorably to the corresponding control values of 0.18% and 0.19% obtained experimentally for the neat benzamide compound (*i.e.*, without any additive present). In other words, a formulation of the benzamide compound containing hydroxypropyl cellulose as an additive (or similarly, D-mannitol, partially gelatinized starch (under the 60°C test conditions), or magnesium stearate as an additive) is comparably as stable as the neat benzamide compound under the conditions tested. In contrast, a formulation of the benzamide compound containing lactose as an additive has a degradation value of 0.55%, which means that this particular formulation (or similarly, formulations involving titanium oxide, light-weight silicic

acid anhydride or magnesium aluminum metasilicate) unfavorably accelerates degradation of the benzamide compound compared to the aforementioned control values of 0.18% and 0.19% (*i.e.*, without any additive present). The continued stability of the active component, (the benzamide compound) in a pharmaceutical formulation is obviously highly desired, especially given the fact that the benzamide compound may comprise as little as 0.001 percent by weight of the tablet or liquid to be administered to a patient. At such low concentrations, even relatively minor rates of degradation of the active benzamide compound may result in a less than therapeutically effective amount of the benzamide compound being delivered to a patient.

As a further example of unexpected results, Table 2 is presented below (and represents a sampling of the data depicted in Tables 2, 3 and 4 in Appellants' specification at pages 12-13).

Table 2. % Degradation of tablets containing a benzamide compound (1.0 mg) + additives

Sample #	60°C air-tight for 4 weeks	80°C air-tight for 3 days
a[1]	1.0	1.3
b[2]	0.7	0.5
c[3]	-	0.4
d[4]	-	0.4
e[5]	4.1	3.0
f[6]	4.5	2.1
g[7]	5.8	5.3

[1] Sample a (60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate)

[2] Sample b (60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate + 0.5 mg of tris(hydroxymethyl)aminomethane)

[3] Sample c (60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate + 0.5 mg of potassium bicarbonate)

[4] Sample d (60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate + 0.5 mg of potassium carbonate)

[5] Sample e (40.6 mg of D-mannitol + 17.4 mg of partially gelatinized starch + 2.0 mg of hydroxypropyl cellulose + 3.3 mg of carmellose calcium + 0.7 mg of magnesium stearate)

[6] Sample f (40.6 mg of D-mannitol + 17.4 mg of partially gelatinized starch + 2.0 mg of hydroxypropyl cellulose + 0.7 mg of magnesium stearate)

[7] Sample g (40.6 mg of D-mannitol + 17.4 mg of partially gelatinized starch + 2.0 mg of polyvinylpyrrolidone + 3.3 mg of carmellose calcium + 0.7 mg of magnesium stearate)

As shown above in Table 2, formulations encompassed by claim 44 (samples b, c and d) exhibit superior properties with respect to the stability of a tested benzamide compound against degradation compared to samples a, e, f, and g, each of which is not encompassed by claim 44. In comparing the stability data among samples a to g, it is evident that samples b, c and d exhibit superior stability against degradation under both of the storage conditions tested (*i.e.*, 60° C air-tight/4 weeks and 80° C air-tight/3 days) than samples a, e, f, and g. For example, under conditions of 80° C air-tight/3 days, samples b, c and d show 0.5%, 0.4% and 0.4% degradation products, respectively, while in contrast, samples a, e, f and g show 1.3%, 3.0%, 2.1% and 5.3% degradation products, respectively. Thus, although all samples contain the benzamide compound, D-mannitol as an excipient, magnesium stearate as a lubricant and carboxymethylstarch sodium or partially gelatinized starch as a disintegrant, the samples b, c and d additionally contain an amino compound and/or an inorganic base as required by claim 44.

In contrast, samples outside the scope of claim 44 (*i.e.*, a, e, f and g) do not contain an additional amino compound or inorganic base. For this reason, samples a, e, f and g are less stable than the samples b, c and d in that they produce a higher percentage of degradation products. Therefore, Table 2 clearly demonstrates the advantage that Appellants' claimed invention provides with respect to the prior art. The prior art, and in particular Suzuki, does not contain any information that would teach or suggest the fact that otherwise stable benzamide compounds may become unstable in pharmaceutical formulations or that would allow differentiation between the desired formulations represented by samples b, c and d versus the undesired formulations represented by samples a, e, f and g. More basically, Suzuki does not

address the problem of degradation of the benzamide compound at any point in its disclosure. Clearly then, Suzuki also does not provide any suggestion to a person of ordinary skill in the art as to how the problem of benzamide degradation may be solved. Accordingly, the knowledge of how particular additives impact the stability of select benzamide compounds and the knowledge of how to prepare stabilized formulations containing these benzamide compounds, as claimed in Appellants' claim 44 is unexpected and could not have been derived from routine experimentation by a person of ordinary skill in the art based on a reading of Suzuki.

Table 3, shown below (and depicted with additional examples as Table 6 in Appellants' specification at page 15) relates to pharmaceutical formulations as encompassed by Appellants' independent claim 46 (*i.e.*, liquid formulations).

Table 3. % Degradation of liquid formulations of 20 mg/mL of a benzamide compound in polyethylene glycol 400 containing an additive at a concentration of 0.05M

Additive	80°C air-tight for 3 days
none	41.4
sodium fumarate	21.6
tris(hydroxymethyl)aminomethane	2.9
diethanolamine	3.9
ammonium carbonate	3.6
potassium bicarbonate	15.5

As can be seen from the data in Table 3, a polyethylene glycol solution of a benzamide compound of formula (1) results in extensive degradation (*i.e.*, 41.4%) of the benzamide compound. However, the addition of an organic acid salt (*e.g.*, sodium fumarate), an amino compound (*e.g.*, tris(hydroxymethyl)aminomethane or diethanolamine) or an inorganic base (*e.g.*, ammonium carbonate or potassium bicarbonate) greatly increases the stability of these solutions, as evidenced by a lower percentage of degradation products as compared to the control

sample. Thus, liquid formulations of benzamide compounds as claimed in Appellants' claim 46 are superior to previously known formulations with respect to their stability against degradation. As discussed above, Suzuki does not address the problem of degradation of benzamide compounds in pharmaceutical formulations, let alone provide hints or suggestions to a person of ordinary skill in the art as to how this problem could be solved. Regarding Appellants' claim 46, Suzuki does not teach or suggest that, in addition to a solvent, the use of an organic acid salt, an amino compound and/or an inorganic base is required to stabilize the benzamide compound. In fact, Suzuki lists (i) polyethylene glycol (page 46 of the description), (ii) sodium alginate (page 46 of the description) as a disintegrator for tablets, and (iii) calcium carbonate (page 46 of the description) as an excipient for tablets. Because Suzuki does not teach the combination of the particular formulations claimed in Appellants' claim 46, Suzuki clearly does not appreciate Appellants' discovery that these particular additives stabilize benzamide compound solutions of polyethylene glycol. Therefore, the increased stability of the pharmaceutical formulations according to Appellants' claim 46 could not have been expected by a person of ordinary skill in the art based on the teaching of Suzuki.

2. Rejection under 35 U.S.C. 103(a) over Suzuki in view of the Dictionary and Handbook

In finding Appellants' claimed formulation obvious over Suzuki in view of the Dictionary and Handbook, the Office Action relies on the Dictionary and Handbook for its teaching of components that the Office Action acknowledges is not taught by Suzuki, such as mannitol or Appellants' claimed amino compounds or organic and inorganic salts.

Appellants respectfully disagree with this asserted rejection. The Dictionary and Handbook mechanically lists approximately 100 specific amino compounds, organic salts and inorganic salts, but does so under the general heading of "pH Adjusters" with no description of the suitability of one pH adjuster over another when combined with a benzamide compound such as those encompassed by Appellants' claims 44 and 46. Thus, the Dictionary and Handbook cannot remedy the lack of teaching or suggestion in Suzuki regarding the destabilizing effects of various additives on benzamide compounds and the requirement in Appellants' claim 44 of a benzamide of Formula (I) or a pharmaceutically salt thereof in combination with an excipient

selected from the group of specifically recited excipients; a lubricant selected from the group of specifically recited lubricants; a disintegrant selected from the group of specifically recited disintegrants; and at least one of an amino compound and an inorganic base selected from the group of specifically recited amino compounds and inorganic bases. The Dictionary and Handbook also cannot remedy the lack of teaching or suggestion in Suzuki regarding the requirement in Appellants' claim 46 of a benzamide of Formula (I) or a pharmaceutically salt thereof in combination with at least one solvent selected from the group of specifically recited solvents; and at least one of an organic acid salt, an amino compound and an inorganic base selected from the group of specifically recited organic acid salts, amino compounds and inorganic bases.

Further, there is no motivation provided by Suzuki for a person of ordinary skill in the art to focus on adding only pH adjusters to a formulation of a benzamide when literally hundreds of other excipients are disclosed in the Dictionary and Handbook as possibly suitable for inclusion in a standard cosmetic formulation.

3. Rejection under 35 U.S.C. 103(a) over Suzuki in view of Savastano

In finding Appellants' claimed formulation obvious over Suzuki in view of the Savastano, the Office Action relies on Savastano for its teaching of components that the Office Action acknowledges is not taught by Suzuki, such as pregelatinized starch, mannitol, amino acids (*e.g.*, glycine) and inorganic salts (*e.g.*, disodium phosphate).

Appellants respectfully disagree with this asserted rejection. Similar to Suzuki, Savastano contains undifferentiated lists of excipients. While Appellants admit that Savastano does list mannitol as suitable additive, Savastano also lists lactose as a suitable additive in the same sentence. As observed by Appellants and as shown above in Table 1, lactose degrades a benzamide compound encompassed by Appellants' claims 44 and 46. Thus, Savastano cannot remedy the lack of teaching or suggestion in Suzuki regarding the destabilizing effects of various additives on benzamide compounds or the particular component requirements recited by Appellants' claims 44 and 46.

Further, there is no motivation provided by Suzuki for a person of ordinary skill in the art to focus on adding a narrowly defined class of non-disclosed additives (*e.g.*, amino acids,

mannitol and pregelatinized starch) to a formulation of a benzamide compound when literally over one hundred other excipients are taught in Savastano as equally suitable for inclusion in the described controlled release drug formulation.

For at least the above stated reasons, Appellants respectfully submit that the subject matter recited by independent claims 44 and 46 is both novel and nonobvious over the teachings of Suzuki alone or in combination with either the Dictionary and Handbook or Savastano. Accordingly, Appellants respectfully submit that the rejections of independent claims 44 and 46 are improper and should be reversed.

B. Dependent Claims 45, 47, 48 and 49

Appellants respectfully assert that dependent claims 45, 47, 48 and 49 are individually allowable at least because of their respective dependencies from independent claims 44 and 46 and for the reasons set forth above. Thus, the rejection of dependent claims 45, 47, 48 and 49 are improper and should be reversed.

Suzuki, either alone or in view of the Dictionary and Handbook or Savastano, does not teach or suggest claim 45, which depends from claim 44 and further limits the composition to D-mannitol as the excipient; magnesium stearate or talc as the lubricant; and partly gelatinized starch, carmellose calcium or carboxymethylstarch sodium as the disintegrant.

Suzuki, either alone or in view of the Dictionary and Handbook or Savastano, does not teach or suggest claim 47, which depends from claim 46 and further limits the composition to polyethylene glycol 400 as the at least one solvent; and a pH in the range of about 7 to about 11 through the addition of an acid or base.

Suzuki, either alone or in view of the Dictionary and Handbook or Savastano, does not teach or suggest claim 48, which depends from claim 47 and further limits the composition to hydrochloric acid as the acid and sodium hydroxide as the base.

Suzuki, either alone or in view of the Dictionary and Handbook or Savastano, does not teach or suggest claim 49, which depends from any one of claims 44 to 48 and further limits the composition to the compound of formula (3) as the benzamide compound.

In view of the foregoing, Appellants respectfully request the reversal of the Examiner's rejections and the allowance of the pending claims. If there are any other fees due in connection with the filing of this Appellants' Brief, please charge the fees to our Deposit Account No. 50-0310.

If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 50-0310.

Respectfully submitted,

MORGAN LEWIS & BOCKIUS LLP

Dated: **February 2, 2007**

By: _____
Gregory T. Lowen
Reg. No. 46,882
Direct: 202-739-5915

CUSTOMER NO. 009629
MORGAN LEWIS & BOCKIUS LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: (202) 739-3000
Fax: (202) 739-3001

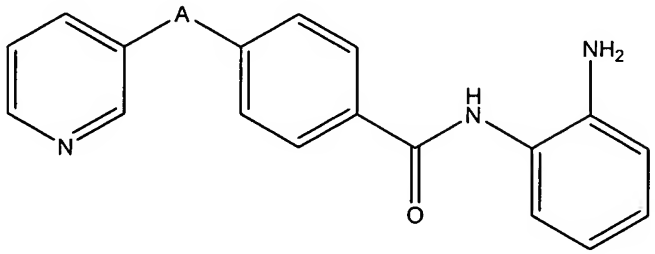
8. Claims Appendix

Subsequent to entry of the Amendment and Response under 37 C.F.R. § 1.114, the claims read as follows:

Claims 1-43 (cancelled).

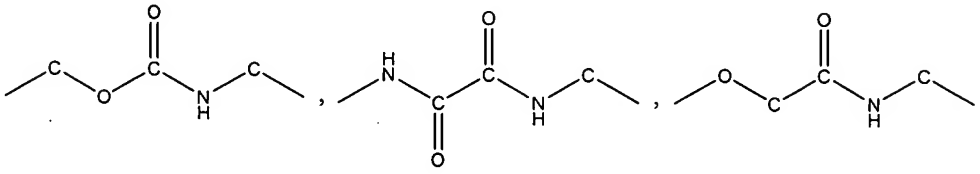
Claim 44. A pharmaceutical formulation comprising:

a benzamide derivative represented by formula (1):



(1)

wherein A represents a structure shown by any one of formula (2):



(2)

or a pharmaceutically acceptable salt thereof;

an excipient selected from the group consisting of lactose, lactose anhydride, D-mannitol, corn starch, and crystalline cellulose;

a lubricant selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, and talc;

a disintegrant selected from the group consisting of partly pregelatinized starch, carmellose calcium and carboxymethylstarch sodium; and

at least one member selected from the group consisting of an amino compound and an inorganic base,

wherein

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

Claim 45. The pharmaceutical formulation according to claim 44,

wherein

the excipient is D-mannitol;

the lubricant is selected from the group consisting of magnesium stearate and talc;

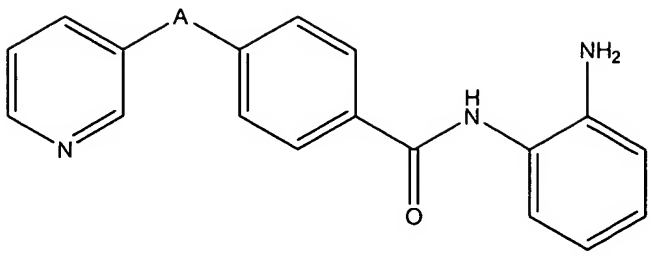
the disintegrant is selected from the group consisting of partly pregelatinized starch, carmellose calcium and carboxymethylstarch sodium;

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

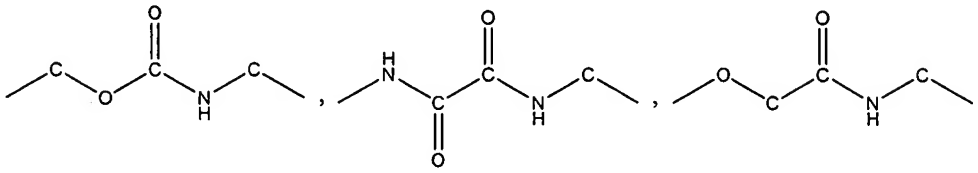
Claim 46. A pharmaceutical formulation comprising:

a benzamide derivative represented by formula (1):



(1)

wherein A represents a structure shown by any one of formula (2):



(2)

or a pharmaceutically acceptable salt thereof;

at least one solvent selected from the group consisting of propylene glycol, dimethylacetamide, and a polyethylene glycol; and

at least one member selected from the group consisting of an organic acid salt, an amino compound and an inorganic base;

wherein

the organic acid salt is at least one member selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

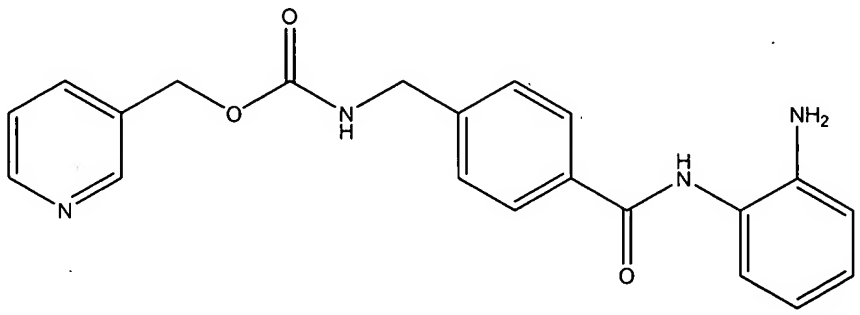
Claim 47. The pharmaceutical formulation according to claim 46 wherein

the at least one solvent is polyethylene glycol 400; and

the formulation is maintained at a pH in the range of about 7 to about 11 through addition of an acid or a base.

Claim 48. The pharmaceutical formulation according to claim 47 wherein the acid is hydrochloric acid and the base is sodium hydroxide.

Claim 49. The pharmaceutical formulation according to any one of claims 44 to 48, wherein the benzamide derivative is the compound of formula (3):



(3)

9. Evidence Appendix

Attached is an inventor declaration under 37 C.F.R. 1.132 by Mr. Masahiro Sakabe, attesting to the significance of the observed data. This declaration was previously submitted to the U.S. Patent Office in a response filed on December 4, 2006 and was entered into the prosecution record as evidenced by the examiner's comments in the Office Action dated January 9, 2007.

PATENT
Attorney Docket No. 054160-5060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Tsuneji Suzuki *et al.***	)	
U.S. Application No. **10/049,666**	)	Group Art Unit: **1615**
Filed: **February 15, 2002**	)	Examiner: **Gollamudi S. Kishore**
Title: **Pharmaceutical Agent Comprising a Benzamide Derivative as Active Agent**	)	Date: December 4, 2006

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, **Mail Stop Amendment**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

DECLARATION UNDER 37 C.F.R. § 1.132

I, the undersigned, Masahiro Sakabe, do hereby declare that:

1. I am a citizen of Japan, residing at 3-8-6-804, Kikukawa Sumida-ku, Tokyo, Japan.

2. I have been awarded a Bachelor's degree in chemistry from the Chiba University.

3. I have been employed by Nihon Schering K. K. since January 1st, 2001 and I am presently a Manager at Nihon Schering K. K.. During my employment at Nihon Schering K. K., I have been engaged in research & development in the area of Pharmaceutics and in-vitro diagnostics.

4. I am familiar with the specification and pending claims of U.S. Patent Application No. 10/049,666. I have reviewed the Office Action dated March 2, 2006 and the Interview Summary dated May 18, 2006. Regarding the data presented in the tables in the specification, I

believe that as an artisan skilled in the art of high-performance liquid chromatography (HPLC), the differences between the listed numbers are statistically significant. For example, Table 1 shows that when D-mannitol and compound 1 are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.21 percent (%) relative to the total amount of compound 1 present in the mixture. This value is comparable to the stability of compound 1 in the absence of any additional component (0.18 or 0.19 depending on the conditions tested). In contrast, when lactose and compound 1 are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.55 percent (%) or 0.44 % relative to the total amount of compound 1 present in the mixture, depending on the particular conditions tested. Given my level of skill in HPLC chromatography, I believe that the difference between, for example, 0.21 (D-mannitol + compound 1) and 0.55 or 0.44 (lactose + compound 1) is statistically significant in that a conclusion may be drawn regarding the stabilizing effects of D-mannitol on compound 1 and the destabilizing effects of lactose on compound 1.

5. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: November 16, 2006 By: Masahiro Sakabe

(Masahiro Sakabe)

10. Related Proceedings Appendix

No information is appended under this section.